vitamin D compounds, their analogs and derivatives. Applicants direct the examiner's attention to U.S. Patents 5237110, 5342975, 5710294, 5587497, 5246975, and 6136799 (copies of which are enclosed for the examiner's convenience) which teach numerous vitamin D compounds *and derivatives* and methods for making these compounds and derivatives. These patents are just a sampling of the detailed literature available to those skilled in the art. Moreover, the specification itself names on page 3 and 4 more than 40 specific vitamin D2 and D3 compounds, including derivatives and analogs, and identifies several other patent literature references (page 4, lines 6-9) which disclose formulations and administration of various vitamin D compounds. Thus, information about these commonly used phrases and this class of compounds (including derivatives and analogs) is readily available and plentiful to those skilled in the art, both in the subject application as well as in the technical literature.

The Office Action also comments that the examples in the specification are not "exhaustive." There is no statutory requirement under Section 112 for "exhaustive" examples. Nor does the patent statute require a specific example for every species embraced by a broad claim. Rather, working examples such as those present in the specification constitute but one *way to satisfy* the statutory enablement requirement. The working examples in the subject application describe procedures by which those skilled in the art can identify ICU-associated hypocalcemia (example 1 and defined at page 3, lines 1-10), induce ICU-associated hypocalcemia (example 2) and treat hypocalcemia with vitamin D compounds and derivatives (examples 3 and 4 according to the invention). As such, these examples provide reasonable assurance to those skilled in the art about the claimed methods of treatment. Therefore, even if the examples are not "exhaustive," the long list of exemplary compounds presented in the specification itself along with the enabling teachings in the voluminous and readily available research and patent literature (as exemplified above) about compounds having "vitamin D-like activity" (the subject application at page 1, lines 8-9) adequately supplement the examples presented in the specification to provide more than the minimum information one skilled in the art would reasonably need to practice the claimed invention without undue experimentation.

This rejection is therefore improper and should be withdrawn.

Claims 1, 3-6 and 8 were also rejected under 35 U.S.C. 112, second paragraph on the basis that these claims fail to particularly point out and distinctly claim the subject matter of Applicants' invention. In particular, the Office Action point to the phrases "vitamin D2 derivatives" and "vitamin D3 derivatives" as not clearly indicating "what additional compounds might also be encompassed" thereby. Applicants respectfully disagree.

Preliminarily, the Office action does not point to any statement from Applicants or other objective information that indicates that some subject matter encompassed by the claims is **not** considered by Applicants to be Applicants' invention. In fact, the converse is true, in view of the long list of exemplary compounds in the specification and the showing that the state of the art is replete with teachings about such compounds and derivatives. Applicants also direct the examiner's attention to the disclosure in the subject application that the invention is directed to treatment of ICU-associated hypocalcemia "by administration of a vitamin D compound, or other compounds exhibiting vitamin D-like activity" (page 1, lines 8-9) and the further statement at page 3, lines 11-22, which states:

> "As used herein, the term "vitamin D compound" encompasses compounds which control one or more of the vitamin D-responsive processes in mammals, i.e., intestinal calcium absorption, bone mobilization, bone mineralization and cell differentiation. Thus, the vitamin D compounds encompassed by this invention include cholecalciferol and ergocalciferol analogs which express calcemic or cell differentiation activity. Without limiting the vitamin D compounds encompassed by the present invention, these synthetic cholecalciferol and ergocalciferol analogs comprise such categories of compounds as the 5,6 trans-cholecalciferols and 5,6-trans-ergocalciferols, the fluorinated cholecalciferols, the side chain homologated cholecalciferols and side chain homologated cholecalciferols, the side chain truncated cholecalciferols, the 19-nor cholecalciferols and ergocalciferols, and the 10,19-dihydrovitamin D compounds."

The scope of the claimed invention is commensurate with the scope of the disclosure.

Moreover, the illustrative use in the patents identified above of the cited phrases clearly shows that those skilled in the art know what these phrases mean. That the phrases "vitamin D2 derivatives" and "vitamin D3 derivatives" can encompass numerous known species in and of itself is insufficient basis for rejecting the claims as failing to distinctly set forth Applicants' invention.

Consequently, this rejection is improper and should be withdrawn.

Rejection under Section 103

Claims 1-9 stand rejected as obvious over Knutson et al (US 5869473) and the ZEMPLAR monograph from the Physicians' Desk Reference previously of record. Applicants disagree for the following reasons:

Vitamin D therapy currently is indicated in two medical conditions: 1) vitamin D deficiency resulting from dietary deficiency (such as malabsorption syndrome) and 2) a deficiency of endogenous vitamin D activation (a two step process involving hepatic 25 hydroxylation, and then 1 hydroxylation in the kidney). The failure of 1 hydroxylation in patients with progressive or end stage renal disease is currently the most common clinical situation in

which active vitamin / vitamin D analogues are employed. Pseudohyperparathyroidism, a rare condition that associates with hypocalcemia and elevations in PTH, also requires therapy with vitamin D.

As illustrated in the first row of the following table, critically ill patients do not have elevations in PTH and vitamin D deficiency. Rather, vitamin D levels tend to be normal, despite the presence of hypocalcemia. The reason for critical illness-induced hypocalcemia is likely multifactorial in nature. However, that PTH and vitamin D levels do not rise in response to a reduction in ionized serum calcium clearly indicates a failure of normal homeostatic mechanisms.

	Serum Ca	Serum P	Serum PTH	Vit D level
Intensive Care Unit-Associated Hypocalcemia	↓	↓→	→	→
Secondary hyperparathyroidism	↓	↑	↑	↓
Vitamin D deficiency	↓	↓	↑	↓
Pseudohypoparathyroidism	↓	↑→	↑	↓

Given the failure of vitamin D levels to rise appropriately in the setting of critical illness, the present invention proposed to provide exogenous active vitamin D to compensate for this lack of a normal compensatory mechanism. Neither the medical literature nor either of the cited references teach or suggest using vitamin D for such a purpose. The absence of guidelines for the treatment of ICU-associated hypocalcemia in the Harrison's Textbook of Internal Medicine further illustrates the novelty of Applicants' proposed therapeutic strategy encompassed in the claimed invention.

The art actually teaches away from Applicants' claimed invention. Current medical practice calls for the administration of high doses (grams) of IV calcium (gluconate or chloride), which carries substantial attendant risks (such as induction of metastatic calcification or arrhythmias). In addition, treatment with exogenous active vitamin D directly addresses a specific deficiency which accompanies the targeted disease state. Current therapy with IV calcium does not do this, as there is no total body calcium deficiency.

As such, the cited references are insufficient to render the claimed invention obvious.

CONCLUSION

Applicants respectfully submit that the subject application is in condition for allowance. The Examiner is urged to contact the undersigned at (847) 937-4558 to facilitate resolution of any outstanding issues.

The Commissioner is authorized to charge to Deposit Account No. 01-0025 any additional filing fees (or credit any over payments) that may be required under 37 C.F.R. § 1.16 and 1.17 in association with this communication for which full payment has not been tendered.

Respectfully submitted,
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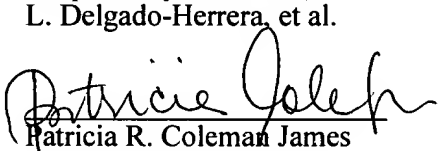

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